UNIVERSITY OF TORONTO
MEDICAL JOURNAL

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DECEMBER 1959

VOLUME XXXVII NUMBER 2

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UNIVERSITY OF TORONTO
MEDICAL JOURNAL

ESTABLISHED DECEMBER 1923
AN UNDERGRADUATE PUBLICATION

VOLUME XXXVII NUMBER 2

TORONTO, DECEMBER 1959

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This Journal is published six times a year from November to April, by the Medical Society of the University of Toronto, to serve primarily as a medium for student expression.

Subscription rates: $3.50 for one volume of six consecutive issues. Single copies 65¢.

Manuscripts including references and footnotes should be typewritten double spaced on one side of the paper. References should be kept to a minimum, and should be cited numerically in the order in which they appear in the text.

Manuscripts in excess of 3,000 words will be considered *unsatisfactory*.

Illustrations are included by arrangement with the Editor. Drawings should be done on white paper in black ink.

Final copy date is the first day of *two months* prior to publication, e.g., September 1 for the November issue.

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Correspondence should be addressed to Room 114, Medical Building, University of Toronto, Toronto 5, Ontario.

Authorized as Second Class Mail, Post Office Department, Ottawa.

EDITORIAL

The adjournment of the 23rd national conference of the Canadian Association of Medical Students and Internes, CAMSI, occasions a few editorial comments on this prominent organization which took its origin in 1936 along with that other controversial organization, the National Federation of Canadian University Students. Like the latter CAMSI has had the many struggles and upheavals common to all embryonic organizations, but CAMSI's seeds have taken firmer root and borne more abundant fruit. Indeed, the status of CAMSI has grown out of proportion to the support accorded it by its members. A more detailed report of the conference is presented below, but we would like to highlight a few aspects of CAMSI that might deserve closer attention by its members.

A function of CAMSI with which most students are familiar is the preceptorship plan which is sponsored in association with the College of General Practice. Under this plan the third year student spends a period of time as the apprentice of a general practitioner who has volunteered to take the student into his home, his office practice and his hospital practice. It is a stimulating experience for the student who is at the peak of his academic training and is hungry for the opportunity to see how this training is put into practice. The experience has also proven stimulating for the preceptor who is refreshed by the new concepts which the student may suggest in their numerous discussions. These men are to be admired for their generous and unselfish co-operation in this plan. The preceptorship is a unique opportunity and the few schools who have such a plan available are hailed as leaders in progressive medical education. We recommend everyone to consider this opportunity seriously and to include it as part of his summer after the third medical year.

Organization of medical students and internes on a national basis has been instrumental in their slow but progressive emancipation from the humble position traditionally accorded them by medical faculties and hospital administrations. CAMSI's policy states that it does not wish to assume "the role of labour union or bargaining agent", but the fact remains that through its efforts medical students and internes have become recognized as definite entities in the medical profession and their problems have become acknowledged as worthy of consideration.

The ideal medical student as typified by Sir William Osler, was the early-to-bed, early-to-rise, non-drinking, non-smoking bachelor who trailed along mutely in the shadow of the professor. However, since that time the character of the medical student has changed; he is now much more independent, he has many more responsibilities and obligations, and he therefore demands that his new position and needs be recognized and appreciated. This change represents a minor social revolution and whether it is good or bad we must accept it and channel it along productive pathways. CAMSI has undertaken to do this and the medical profession realized this when the Canadian Medical Association invited CAMSI to become officially affiliated with it. More specifically CAMSI has achieved great success in the field of interne placement and remuneration; in student aid in the form of scholarships and bursaries, and books, instruments and life insurance at reduced prices; in income tax exemption and in summer employment.

It would appear that CAMSI is concerned only with the material welfare of its members, but this is not so. Medical education is another field of CAMSI endeavour, through its student forums and the annual lectureship on medical education. Past achievements include the combining of final year examinations

with the Dominion Councils, the distribution of free examination reprints, the student exchange, and many others. The less prominent interests of CAMSI are multiple and are well set forth in the small history and Constitution soon to be distributed to all its members.

We recognize CAMSI as a valuable and useful organization and we urge you to join with us in giving it your strong support.

The Keen Man

"There be two kinds of keen men. The one keepeth his keenness unto himself, and publisheth it not upon the roof tops; him do we admire and emulate. The other striveth ever to be in the front row, and taketh copious notes therein; the scratching of his pen is a burden unto the lecturer. . . . At lunchtime he eateth buns in a white garment. . . . He carryeth not his stethoscope in stealth, neither doth it shame him that he talketh shop in strident tones to his brethren in the public places of the city. Regard him closer; from his fancy vesting protrude his scissors, his drug book, his Scott's Emulsion Diary; thus may ye know him. He feareth not the scowls of the clerks, but burroweth himself ever into the foremost rank, whence he cocketh his head at the physician, saying: 'Yea, yea, verily it is praesystolic.' Of the surgeon he asketh intelligent questions, while yet he already knoweth the answer. He runneth up to the moribund patient, and bangeth him upon the chest. . . . He taketh of the dust from the library shelves, and depositeth it upon the cloak-room towels. And when he hath diplomated he goeth forth crying: 'Of a verity am I out of touch with the student lads.'"

—N.G.H. St. Bartholomew's Hospital Journal, 1905

MEDICAL RESEARCH AT THE UNIVERSITY OF TORONTO (PART I)

W. N. DALE, 6T1

Introduction

As medical students, we often think that the Faculty of Medicine revolves about the student and that the training of young doctors is its most important function. In a university the size of ours, however, the establishment and carrying out of a research program is an equally important role. This program is one that the medical student has little chance to see or understand. Yet each day we must of necessity pass by doors behind which the very research is going on that we will read about next week in lay magazines.

This year, the editorial staff of the Journal is publishing a comprehensive outline of some of the research being carried out within the Faculty of Medicine of this university. We hope that some of this material may serve to implant new ideas and stimulate enthusiasm for careers in medical research. Through the printing of this article, the Journal staff wishes to pay tribute to all those gifted people who, by their investigative ability, enterprise, and tenacity of purpose, are progressing toward new heights in the understanding, treatment, control, and eradication of disease. It is through their tireless efforts that the medical student is provided with a living stream of knowledge and not a stagnant pool from which to drink.

In order to avoid a maze of detail, the material will be presented as briefly as possible, leaving the finer points for interested individuals to seek out for themselves. The first articles include the more basic, unglamorous but essential groundwork carried out in the Departments of Pathology, Physiology, Pharmacology and Biochemistry. Later in the year, the research programs in the Departments of Medicine and Surgery will be outlined—the kind that the enthusiastic but often under-informed press enjoy reporting. It must be emphasized that this article cannot include all the medical research that is in progress at the university.

We have been greatly impressed by the co-operation and the many helpful suggestions afforded us by departmental heads and staff. Throughout most of the research, an attempt has been made to correlate closely laboratory research with clinical studies. As we plan to point out later, the tedious nature of the work in many experiments is almost unbelievable. There is a continual interchange of ideas and material aid between departments. New additions in the form of highly trained personnel and expensive apparatus are constantly being procured to "step up the pace". In each department we found the research to be in extremely skilled hands, resourceful enough to carry out their program with the material and funds available, and patient enough to work on the same project for years without any great assurance of ultimate success.

Department of Pathology

Much of the current research being undertaken in the Department of Pathology at the Banting Institute owes its inspiration to Dr. J. D. Hamilton and stems from certain basic investigations which he carried out at Johns Hopkins University in Baltimore and in Cambridge, England. The various projects cover the broad topics of allergic inflammation with emphasis on renal and hepatic lesions. Clinico-pathologic investigations of "auto-immune" phenomena are also in progress particularly with reference to the thyroid gland. The ultimate aim is to form within the Department a competent research unit capable of dealing with the complex problems of immunopathology. Close co-operation is presently being established with Dr. T. F.

Nicholson of the Department of Pathological Chemistry and with the immunochemical investigation unit of the Hospital for Sick Children.

Various human renal diseases are being studied by means of light, fluorescent and electron microscopy, with particular emphasis on clinico-pathologic correlation. Simultaneously, experimental renal lesions are being produced in animals for study as prototypes for the understanding of the pathologic changes in human glomerulonephritis. Rabbits and sheep are being injected with dog kidney and the resulting rabbit and sheep anti-dog kidney antisera re-injected into dogs, where the resulting "nephrotoxic" nephritis is being studied. The relatively recent introduction of fluorescent microscopy enables the investigator to localize the fluorescent-dye-tagged antibody as well as the antibody produced in the dog in response to the renal injury. The site of the antigen-antibody interaction can be localized and correlated with morphologic changes. The electron microscope is being used in these investigations to resolve certain problems of ultra-microscopic localization of lesions and their fine structure which were hitherto unrecognized.

By means of these studies, combined with investigations of the biochemical and immunologic changes, they hoped to throw some light on the pathogenesis of those renal lesions which are suspected of having an allergic aetiology.

An investigation is in progress to establish prototypes of immunologic injury of the liver and thereby attempt to throw some light on those hepatic lesions, such as primary biliary cirrhosis, which are thought to have an allergic basis.

In an attempt to elucidate the basic injury produced by antigen-antibody interaction, experiments are being carried out which are intended to test the pathogenic potential of antigen-antibody complexes formed *in vitro* and subsequently injected into animals.

Other research activities in the Department of Pathology are proceeding along several separate and distinct lines. It is hoped that the long-term study of the pathogenesis of coronary thrombosis and of peripheral vascular disease in diabetics and non-diabetics will be completed this year. Studies into the pathogenesis of the renal changes in hydronephrosis and allied conditions are continuing. Demyelinating diseases are being investigated by histologic means in the spinal cord, brain, and peripheral nerves. In the division of Neuropathology, studies of the blood-brain barrier are to be started very soon.

In collaboration with the Department of Surgery a study of malignant cells in the venous drainage from tumours before, during, and immediately following surgery has been undertaken.

Morphological studies of the calcification of bones in various metabolic diseases are continuing with emphasis on establishing the normal range of histologic patterns.

Charles H. Best Institute

Ever since Banting and Best made their epic discovery of a method for isolating the pancreatic antidiabetic hormone insulin, many of the research facilities of this university have been devoted to the study of both the diabetic state and more generally to all phases of metabolism. So much work has been done along these lines since that time that to-day Toronto stands as one of the foremost metabolic research centres in the world. It is indeed a great tribute to the director and his staff that Toronto has been able to maintain the prestige it gained some 35 years ago when insulin was first isolated.

The more basic the research, the closer one must approach the basic laws of physics and chemistry, and of course this brings one closer to the secrets of life itself. Because of the basic nature of some of this work it is difficult to describe it adequately in an article of this length.

Workers here have devised a new method for the calculation of transfer rates of various metabolites into and out of metabolic compartments. This method leaves out many of the assumptions of previous methods and has been acclaimed both here and at other centres as a solid step ahead in this field. For example, critical studies using isotopically-labelled tracer methods are being carried out to measure the effect of insulin on the glucose space and on rates of glucose transfer into and out of the plasma compartment in normal, depancreatized and depancreatized-adrenalectomized dogs. The studies would indicate that insulin increases the peripheral uptake of glucose, and that the effect of the adrenalectomy is mainly a central one—that of decreasing the glucose output from the liver when compared to the normal and depancreatized animals.

Other available tracer methods can be used for rate determinations of phosphorus, sodium, potassium, iron etc. The effects of thyroid activity on the rates of phosphorus transfer throughout the rat is now under study. When these experimental methods have been perfected in animals, it is hoped that they may be applied to the study of human physiology and later to the study of human disease states.

There has been a good deal of theory developed in regard to metabolic transfer rates which I will briefly mention. We all remember the "closed" chemical equilibrium $A + B \rightleftharpoons C + D$. In living systems, we have a similar equilibrium present except that it must be termed "open" because we are continually making exchanges with our environment, e.g. $(X \rightarrow A + B \rightleftharpoons C + D \rightarrow Y)$. If you think for a moment about the dynamic state of the bodily constituents, you must of necessity consider your arm, eye, liver etc. merely as expressions of the metabolites that are passing through them. As the Greek philosopher Heraclitus once said, "You cannot step into the same river twice because fresh water is always flowing toward you." What does this all mean in terms of practical application to human disease? As yet this question cannot be answered. What workers would like to do is to bring the time factor into their calculations or in other words discover more about metabolic kinetics in various disease states. For example we learn that the average range of fasting blood sugar is 60–105 mg. %. Patients A and B may have similar blood sugar levels, but the rate of turnover may be entirely different in each patient. This work on metabolic kinetics is the difficult, time-consuming type of labour that lays the groundwork for the "miraculous" discoveries reported in the lay press.

Studies have just begun which are hoped to lead to further knowledge about the cause of atherosclerosis. Considerable theory has been advanced along this line in recent years. Many workers have suggested that the primary disturbances are in lipid metabolism and blood coagulation. Duguid's theory is that fibrin is first laid down on vessel walls. Vascular endothelium then proliferates and covers this fibrin over. In this process then, the fibrin actually becomes incorporated into the intima. Later this fibrin becomes impregnated with lipoid materials and cellular elements. If this theory is true, the question arises as to what changes in the clotting mechanism were responsible for the initial laying down of fibrin. Some workers have suggested that there is a constant deposition of fibrin on vessel walls which is continually being broken down by fibrinolysin. They think of a delicate balance existing between fibrin deposits and fibrinolytic activity. It may be that increased fat levels partially inhibit the action of the enzyme fibrinolysin. It is hoped that by a careful study of the interdependence of coagulants and anticoagulants some of these questions may be answered.

Hahn and Weld in 1943 observed that

heparin when injected into an animal, had the ability to clear fatty plasma very quickly. This action was not present *in vitro* and it suggested that heparin did not act on fat directly. It was later found that if heparin was injected into a normal dog, and subsequently if the dog's plasma was added to lipemic blood, the latter would clear. It has been found that heparin releases a lipase capable of splitting triglycerides into fatty acids and glycerol, and that this lipase is normally present in some plasma. The relationship of this enzyme to fat transport is at present being investigated at the Best Institute. Perhaps people with atherosclerosis have a low content of this enzyme resulting in high blood lipid levels.

GLUCAGON

Glucagon was discovered in 1923 shortly after Banting and Best's discovery of insulin. It was noted that injections of insulin were followed by a transient increase of blood sugar before the characteristic decrease of blood sugar took place. Murlin and Kinball, two U.S. investigators, postulated that a separate substance was present with insulin in the pancreatic extracts and they named this substance glucagon. The separate existence of glucagon was established by Buerger and his colleagues in Germany in 1928 and later work has shown it to be a single chain polypeptide of different molecular structure to insulin. It has only been isolated in crystalline form since 1953.

Site of Production

Evidence has been accumulating for many years that glucagon is manufactured and released from the pancreatic alpha cells. It was felt that if this were true, compensatory atrophy of these cells should be evident in animals that have received excessive amounts of glucagon. Several cytochemical and histological techniques for examining the islets of the rabbit pancreas have been perfected here and provide convincing evidence on this same point. When the normal pancreatic islets of the rabbit are stained appropriately, the pink staining alpha cells can be seen about the periphery surrounding the more central beta cells which stain blue. In control rabbits the large and sharply defined nucleus surrounded by abundant cytoplasm can be seen. The effect of 10 days of glucagon treatment on the alpha cells, is to produce nuclei which are denser, smaller and not so well demarcated as those in the controls. The most striking feature is the absence of cytoplasm. It would appear then that glucagon does produce an atrophy of the alpha cells. It has been postulated that the alpha cells are part of a homeostatic mechanism for the regulation of blood sugar levels. This theory suggests that if the blood sugar level falls, through the action of insulin, glucagon is released to raise it. If this were true one might expect that too much glucose in the blood would lead to atrophy of the alpha cells just as too little sugar produces atrophic changes in the beta cells. When animals were overloaded with sugar for 21 days there was no evidence of any reduction in the activity of the alpha cells. Neither sustained hypoglycemia or hyperglycemia appear to alter the histochemical or histological characteristics of the alpha cells. These observations are not in keeping with the hypothesis that glucagon plays an important role in the maintenance of normal blood sugar levels.

Glucagon Diabetes

Workers here have succeeded in inducing prolonged diabetes in rabbits as a result of injections of glucagon several times daily from infancy for a period of some five months. Originally, nothing more than a temporary diabetes could be produced with glucagon. Although this is an extremely interesting experimental observation, the significance of glucagon in the genesis of diabetes cannot yet be evaluated.

Metabolic and Diabetogenic Effects

This work may have important implications far beyond diabetes. For besides its proven ability to produce diabetes in animals, workers in the Department of Physiology have also been struck by other metabolic activities of this substance in experimental animals. Besides producing hyperglycemia, glycosuria and a rapid weight loss, previous work has shown that there is also an increased urea excretion. The increased nitrogen output suggested a more rapid gluconeogenesis. A more detailed study of this phenomenon was undertaken here under conditions where only a very transient hyperglycemia and no glycosuria occurred. The blood amino acids fell much more rapidly in the glucagon-treated animals and remained lower throughout the five-hour observation period. It does not appear that the glucagon-induced fall in blood amino acids can be attributed to an increase in the rate of peripheral utilization, since urinary nitrogen excretion increased during this five-hour period. The fasting glucagon-treated animals excreted about 40% more nitrogen than the controls. These results indicate that the increase in nitrogen excretion was not dependent upon the production of the diabetic state. In some respects the changes induced by glucagon administration are similar to those produced by adrenal glucocorticoids. The possibility that the marked increase in gluconeogenesis following glucagon treatment was due to stimulation of the adrenal cortex was investigated. The total nitrogen excretion by glucagon-treated and control adrenalectomized rats was studied. It was found that the glucagon-treated adrenalectomized rats excreted about 50% more nitrogen and urea than the controls. At the Best Institute some evidence has been obtained that the effect of glucagon on urea formation is a direct action on the liver since the addition of glucagon to liver slices produces a consistent increase in urea production. The results of these experiments indicate that the catabolic action of glucagon is not necessarily mediated by the adrenal gland. Although the mechanisms are undoubtedly different, the qualitative effects of glucagon and cortisone on protein metabolism are similar since both stimulate gluconeogenesis and decrease body protein.

Substances or conditions which impair the utilization of amino acids frequently cause inflammatory processes to subside. This effect on inflammation may occur because many of the processes involved in its production, such as formation of antibodies, fibrin and granulation tissue, are dependent upon protein anabolic processes. Therefore, it was thought that glucagon might possess anti-inflammatory properties because it reduced protein synthesis and that, if this were true, it would offer certain therapeutic advantages over the steroids because glucagon has no effect on electrolyte metabolism. To explore this possibility, repeated intravenous infusions of glucagon were made in a series of eight patients suffering from rheumatoid disorders. These studies, which were undertaken in collaboration with the Department of Medicine were designed primarily to investigate the effect of glucagon on inflammation, but they also provided an opportunity of studying the metabolic changes produced in human subjects. The effect of glucagon on rheumatic patients was as dramatic as that frequently observed following the administration of cortisone or ACTH. Although glucagon promptly relieves the signs and symptoms of some cases of acute arthritis it is useless as a therapeutic agent. It does not have the same side effects as cortisone but it has serious ones of its own, and its clinical use is not warranted. All of the patients complained of anorexia and nausea and vomiting frequently occurred. These disconcerting side effects preclude its

use as a therapeutic agent. It is possible that an antidote for the side effects may be discovered.

The observations described above indicate that the action of glucagon is predominantly catabolic, and thus far workers here have invariably found it to be a potent growth inhibitor. This property has led Toronto workers to study its effect on the growth of malignant tissues. It was found that when rats bearing the Walker carcino-sarcoma were treated with glucagon, growth of the tumour was reduced from 20–40%. This inhibition could be attributed, in part, to the reduction in food intake and the adverse effect of glucagon on the growth of the rat as a whole. It has been previously known that the administration of insulin to animals on a fixed food intake produced a small but significant inhibition in the growth of transplantable tumours. In the next investigation both insulin and glucagon were administered to rats bearing the Walker carcino-sarcoma. The tumour-bearing rats treated with both hormones lost much less weight than animals given glucagon alone, but an inhibition of tumour growth of 60–70% was observed. The tumours in the untreated controls were obvious, while those of the animals treated with both insulin and glucagon were barely discernible. In each experiment using the Walker carcino-sarcoma, the carcinostatic action of combined insulin and glucagon therapy was much greater than the sum of the individual effects of the two substances. It appears, however, that in other tumours glucagon alone is as effective as glucagon-insulin therapy.

The sum of these properties of glucagon suggests that it plays an important role in body metabolism, and that further study will greatly increase knowledge of how metabolic processes are controlled.

Summary

We have briefly outlined some of the work being done in the Departments of Pathology and Physiology. Again we must stress that this report is of necessity incomplete and that space and time prevent us from mentioning the many other projects that are being carried out. A further report of medical research at the University of Toronto will appear in subsequent issues.

Ocular Trauma:—

Penetrating injuries of the eye are easily missed since they are usually painless initially. If immediate antibiotic treatment is not undertaken a tragic panophthalmitis is the common result.

Infertility:—

Infertility may be psychogenic in origin. A number of cases investigated by Dr. A. Herbert Marbach, Assistant Professor of Gynaecology at the University of Pennsylvania, were found to have no organic basis for their infertility and responded to psychiatric care. The psychological mechanism which he postulates is a persistent Oedipal state in which the wife, who has once desired her father, substitutes her husband for her father and regards their relationship as an incestuous one.

State of Mind, August–September 1958.

THE SIGNIFICANCE OF PULMONARY HYPERTENSION*

B. S. GOLDMAN, 6T0

Introduction

This discussion is concerned with the element of pulmonary hypertension as it influences the treatment and affects the prognosis in certain of the more important cardiovascular and pulmonary diseases. It will be necessary to review the hemodynamic mechanisms that bring about an increase in the pulmonary vascular resistance, so that the importance of this factor as a complication of disease or as an integral part of it, can be fully appreciated. At this time it will also be advantageous to classify pulmonary hypertension in terms which have an important bearing on our clinical evaluation and management.

1. Passive pulmonary hypertension—left heart failure.
2. Vasoconstrictive pulmonary hypertension—mitral stenosis.
3. Hyperkinetic pulmonary hypertension—congenital defects.
4. Obstructive or obliterative pulmonary hypertension—cor pulmonale.

The clinician suspects pulmonary hypertension when the patient experiences dyspnoea on exertion, associated with a prominent pulmonary second sound, radiological evidence of enlargement of the pulmonary trunk and its main branches, EKG evidence of right ventricle hypertrophy, and perhaps a Graham-Steell murmur.

Left Heart Failure

Any one of the numerous causes of left heart failure can lead to a state of *passive* pulmonary hypertension. In these conditions, the increase in left auricular pressure is transmitted to the pulmonary venous system. The increase in pulmonary arterial pressure that results, is merely a reflection of attempts to maintain the normal pressure gradient of 10 mm. Hg. through the lungs. Many of these are acute situations, and there is no increase in the pulmonary vascular resistance if a normal gradient is maintained. Thus the pulmonary hypertension is incidental, and adequate treatment of the underlying pathology is indicated.

Mitral Stenosis

In contradistinction to the passive form, *active* pulmonary hypertension implies a high pulmonary vascular resistance and thus a pulmonary arteriovenous pressure gradient much above the normal. Mitral stenosis of sufficient degree will bring about an increase in the pulmonary vascular resistance; this is possibly due to a persistent pressure of 50/25 mm. Hg. or repeated episodes of pulmonary hypertension of a much higher degree, bringing about a reflex vasoconstriction of the pulmonary arterioles. These conditions of persistent elevation or repeated elevations are not usually seen in other causes of increased left auricular pressure. In mitral insufficiency the mean left auricular pressure and pulmonary venous pressure is less than in stenosis. Thus it would seem evident that there is a critical level of passive pressures which must be reached before the active element ensues.

There is evidence to suggest that in many cases, extremely high pulmonary vascular resistance does *not* develop slowly over the years, but rather develops relatively suddenly before pulmonary congestive symptoms materialize; and indeed, this may well prevent and protect the pulmonary venous system from high pressures and the complications that are attendant upon this: pulmonary oedema, orthopnoea and paroxysmal nocturnal dyspnoea. This development of a high pulmonary arteriolar resistance, due initially to vasoconstriction actually

*From a paper presented to the Alpha Omega Alpha Honour Medical Society, March 1959.

helps to prolong life by preventing the build-up of dangerously high left atrial pressures—but it does this at the expense of the cardiac output and ultimate right heart failure. These cases of high resistance are especially prone to phlebothrombosis and secondary pulmonary embolism which is often fatal, either due to its size or by precipitating right heart failure.

Passive pulmonary hypertension also occurs in mitral stenosis, and when associated with auricular fibrillation it may very well cause right ventricular failure. Thus in the management of a case of mitral stenosis with high pulmonary hypertension, before surgery is contemplated, continuous anticoagulant therapy is indicated. When incipient or frank right heart failure is present, rapid recovery on proper treatment will be seen if it is due to auricular fibrillation and passive hypertension; but if it is due to a high pulmonary vascular resistance, improvement will only be temporary unless valvotomy can be performed.

With regard to the selection of cases for operation, it is a fallacy to believe that active pulmonary hypertension is completely irreversible in mitral stenosis, and that once it is established it acts as a limiting factor in eligibility for commissurotomy. On the contrary, it is an indication for operation. The increased pulmonary vascular resistance may very well mask the severity of a stenosis by inhibiting pulmonary venous congestion —but it is important to remember that resistance is never raised unless the stenosis is critical. Therefore operation is recommended in all such cases, and if the resistance is extreme, surgery becomes an urgent matter due to dangers of phlebothrombosis and heart failure.

In an analysis of results, Paul Wood states that in all the above cases, the arteriolar resistance dropped appreciably following successful surgery and that congestive failure has proven *reversible*. However, from 1952 to 1955 the surgical mortality in uncomplicated cases of simple mitral stenosis was only 1.7% whereas in cases with an extreme pulmonary vascular resistance, mortality was 33%.

Congenital Cardiovascular Defects

Hyperkinetic pulmonary hypertension is a part of many cardiovascular anomalies, particularly atrial and ventricular septal defects, and the patent ductus arteriosus. In these congenital shunts there is an increased blood flow through the lungs. This does not at first produce any increase in pressure due to the great distensibility of the pulmonary vascular bed, but as the flow reaches 2 to 3 times the normal (i.e. up to 15 litres per minute) maximum vasodilation is reached, and further increases in flow produce increases in pulmonary pressure. In certain cases, the added factors of the transmission of left ventricular pressure plus a reactive pulmonary vasoconstriction, ultimately brings on sclerotic changes and very high increases in pulmonary vascular resistance.

ATRIAL SEPTAL DEFECT

In the commonest type of atrial septal defect, the ostium secundum, the pressure in the right ventricle and pulmonary artery of children rarely exceeds 50 mm. Hg. In adult life, however, there is more often an increase in vascular resistance. In an atrioventricularis communis or ostium primum, greater flows and higher pulmonary resistance are commonly found. Pulmonary vascular resistance is usually normal in children, and thus death rarely occurs in infancy or childhood. Skillful surgery can easily remedy the defect. However, in those cases who do present with pulmonary hypertension and a low pulmonary blood flow, one cannot expect relief of the pulmonary hypertension by surgery, because of the already fixed increase in pulmonary vascular resistance. The great problem is to differentiate those that are reversible and those that are not reversible. Calculations of pulmonary

blood flow are therefore important. The added difficulties of a reversal of shunt will be discussed below.

Fortunately most children with an atrial septal defect have a low pulmonary artery pressure and a low resistance which permits corrective surgery with excellent results.

PATENT DUCTUS ARTERIOSUS

In a patent ductus arteriosus, there is a continuous aortico-pulmonary shunt since aortic systolic and diastolic pressures are both above pulmonary pressures. This naturally produces an increase in the pulmonary blood flow, but it is uncommon to find much alteration in the pulmonary artery pressures. This is usually attributed to the limited size of the ductus and the distensible pulmonary vascular bed. Nevertheless many cases do present with pulmonary hypertension, either due to the left ventricular failure, an excessive pulmonary flow due to a short, wide ductus, or an increased pulmonary vascular resistance due to constriction or structural changes. These cases tend to fall into three main groups:

1. *Symptomatic infants*

These present with a failure to thrive and a systolic murmur. The pulmonary artery pressure in systole is equal to systemic pressure. Despite the high pressure, these infants do well with modern surgery since their shunt is still predominantly left to right.

2. *Adults with progressive pulmonary hypertension*

These are patients who originally presented with the continuous murmur of an isolated ductus, but they have demonstrated, with increasing age, the disappearance of the diastolic element of the murmur. The pulmonary hypertension has obviously resulted from prolonged aortico-pulmonary shunting. These cases initially have a left to right shunt, then bi-directional, and then possibly predominantly right to left shunting through the ductus. Adults with a predominantly left to right shunt do well, but cases with marked pulmonary hypertension and bi-directional flow may not fare as well. They should have a thoracotomy and, if, after a temporary trial occlusion of the ductus, the pressure in the pulmonary artery drops, then permanent ligation is indicated. (If it does not drop then the changes in the lungs are contraindications to ligation.)

3. *Lifelong pulmonary hypertension*

This group includes patients of all ages who have had severe hypertension from early life with a predominant reversal of flow through the shunt. In these cases, and in the bi-directional shunts that show poor results after trial occlusion, ligation is contraindicated. If closure were attempted it would remove the safety valve of the pulmonary circulation and the physiological situation would then be akin to primary pulmonary hypertension.

VENTRICULAR SEPTAL DEFECT

This defect varies in severity from the mildest form, maladie de Roger (isolated ventricular septal defect), to ventricular septal defect with pulmonary hypertension to Eisenmenger's complex. From the hemodynamic viewpoint we have four groups of children, depending on the size of the defect and the degree of pulmonary vascular resistance which is established.

1. A small defect and normal, or close to normal blood flows and pressures, 60% of all cases. These children lead essentially normal lives, and live well into adult life, their chief worry being endocarditis.

2. Considerably increased flows through the defect but with only a slight to moderate vascular resistance and pressure. A few of these children go into failure and die in infancy, but most survive and may or may not develop pulmonary hypertension over the years.

3. Those with definite pulmonary hypertension and some increase in pul-

monary vascular resistance, with various degrees of excessive blood flow, but *no* cyanosis. These cases are likely to go into heart failure and die rather early.

4. Those with marked pulmonary vascular resistance, reduced flow through the lungs and some reversal of blood flow through the defect, bringing about varying degrees of oxygen unsaturation in the arterial blood. This group constitutes the Eisenmenger complex. Paradoxically they are likely to get along well in childhood and may run and play actively for years, but are liable ultimately to develop cyanosis.

With regard to considerations for surgery, the first two groups with no or slight pulmonary hypertension need only medical therapy and should wait for better operations to be developed. Those cases most suitable for surgery are the ones with a large blood flow to the lungs, with a relatively low pulmonary vascular resistance and who are over two years of age.

It is perhaps interesting to compare the three anomalies under discussion. Pulmonary hypertension with a markedly increased vascular resistance is rare in a child with atrial septal defect; it occurs in only 5% of cases of patent ductus; but it is present in 15% of the ventricular septal defects.

EISENMENGER'S COMPLEX

The influence and importance of pulmonary hypertension on the ventricular septal defect can be better seen by a more detailed account of the Eisenmenger complex. This was originally described as a ventricular septal defect with a reversed shunt in the absence of any pulmonary stenosis, attributed to an overriding aorta. This is now defined as pulmonary hypertension with a reversed interventricular shunt and the displaced aorta is incidental.

The physiological situation in Eisenmenger's is actually not too bad: the systemic pressure resistance tends to prevent too great a right to left shunt, and so ensures a fair pulmonary blood flow. At the same time, the high pulmonary resistance does not overburden the right ventricle because the ventricular septal defect acts as a safety valve.

The high pulmonary vascular resistance seems to be established at birth. In a child with an isolated ventricular septal defect equal in size to the ventricular septal defect of an Eisenmenger's complex, the foetal vascular resistance drops to normal in the first two weeks after birth and there is a greater risk of death from heart failure then in a child with an Eisenmenger's complex, since the right ventricle in the former cannot tolerate the burden of such a large left to right shunt. The reason for the high resistance in an Eisenmenger's complex is not known; possibly it is due to the persistence of the foetal musculature on which is superimposed hyperkinetic pulmonary hypertension.

The Eisenmenger's reaction can also occur in an atrial septal defect or in a patent ductus arteriosus. But the atrial septal defect has greater variations in size and pressure differences, while the ductus has stricter limits to size, than does the ventricular septal defect, i.e. more cases of ventricular septal defect depend on the Eisenmenger reaction to prolong life than does the patent ductus or atrial septal defect. The prognosis of the Eisenmenger's complex is therefore fair and better than that of the average ventricular septal defect with pulmonary hypertension alone.

It is important to understand that surgery is definitely contraindicated in all forms of the Eisenmenger's complex, because it not only fails to relieve the pulmonary hypertension, but it also removes the safety valve of the pulmonary circulation. It is even more important to understand that pulmonary hypertension due to an increased pulmonary vascular resistance is not a contraindication to the ligation of a ductus or the repair of an atrial septal defect, provided that the pulmonary blood flow is still elevated

and the left to right shunt is still dominant, for the resistance can be expected to fall if the pulmonary blood flow is brought to normal.

Primary Pulmonary Hypertension

An important point in the management of this patient is to confirm the diagnosis of primary, idiopathic or essential pulmonary hypertension by such diagnostic techniques as cardiac catheterization and angiocardiography. For if the hypertension is secondary, then depending on the cause, there may be a possibility of cure. Usually it is not difficult to ascertain whether or not the increased pressure is primary or secondary. It may not be so easy in some cases of disseminated lupus erythematosus, periarteritis nodosa, or schistosomiasis. It is important to note that few, if any, early cases of primary pulmonary hypertension have ever been reported as definitely diagnosed. The average duration of life from the onset of symptoms in 20 fatal cases studied was 3.2 years.

There is no effective treatment for primary pulmonary hypertension. It is true that acetylcholine, Priscoline and aminophylline when injected into the pulmonary artery directly, do lower pulmonary vascular resistance; however, this is obviously impractical therapy. Priscoline, aminophylline, etophylate and hexamethonium have all been tried systemically, but to no avail. The use of steroids has been disappointing; however, they may be of some use if the underlying pathology is some reactive arteritis. There has even been an attempt to provide an outflow safety valve for the pulmonary artery by a Blalock operation (subclavian-pulmonary anastomosis) but the patient died during surgery.

The present management is grossly inadequate. It consists of a combination of strict bed rest or total inactivity, Priscoline, aminophylline or theophylline and Ansolysen. Permanent anticoagulant therapy is also instituted on the chance that recurrent multiple thrombo-embolic phenomena are responsible for the increased vascular resistance. When right heart failure occurs it should be vigorously treated in the usual manner.

Cor Pulmonale

Although we have already included right heart failure as a complication of many cases of pulmonary hypertension, the term cor pulmonale is reserved for a specific cardiovascular disorder secondary to actual disease of the lung parenchyma. The two great factors in the pathogenesis of cor pulmonale are hypoxia and obliteration of the pulmonary vasculature. The degree to which each contributes determines the clinical features, course, treatment and prognosis.

Hypoxia is most commonly seen in emphysema (diffuse obstructive) and is aggravated by attacks of bronchitis, bronchial asthma and bronchopneumonia, the conditions which originally brought on the emphysema. The defect in emphysema is primarily ventilatory resulting in a lowered arterial oxygen tension and a retention of carbon dioxide. However, hypoxia also occurs due to interference with gaseous diffusion across the alveolar-capillary membrane. The defect in diffusion results in lowered arterial oxygen content, but without carbon dioxide retention, due to the far greater diffusibility of carbon dioxide. Hypoxia contributes to pulmonary hypertension by bringing about certain compensatory mechanisms: increased blood volume and viscosity (polycythemia), increased cardiac output (hyperkinetic effect) and also a physiological vasoconstriction. When an acute episode is superimposed upon chronic emphysema, the resultant marked hypoxia causes such a burden on the right heart as to bring on congestive failure.

The second factor, obliteration of a sufficient cross-section of the pulmonary vascular bed to raise the pulmonary artery pressure at rest, is uncommon in

emphysema, but relatively more common in diffuse scarring or fibrosis of the lung. Much of the obliterative element may also come from the reactive pathological changes in the vessels due to a long-standing pulmonary hypertension.

Since the aforementioned facts are so important in determining the principles of treatment, let me summarize briefly by stating that in pulmonary hypertension of chronic disease of the lung parenchyma, hypoxia and vascular obliteration are of prime importance. In emphysema, hypoxia is predominant, and thus if this is alleviated, there will be a reversible component to the pulmonary hypertension. In fibrotic diseases of the lung, obliteration is predominant, and once this has been established, steady deterioration is inevitable. Thus in this latter condition, once the symptoms have been diagnosed, there is little that can be done in the form of prevention or cure, treatment being directed only at the congestive failure. The prognosis is very poor.

The outlook in chronic anoxic cor pulmonale due to emphysema, though by no means good, is considerably better than in pulmonary fibrosis. It is also true that once cardiovascular manifestations arise, the emphysematous patient is much advanced in his disease. But with newer and more effective methods of investigation, circulatory involvement should be recognized before the onset of failure. The pulmonary changes are, of course, irreversible, but the physician who takes advantage of the reversible element of emphysema can do much to prolong the life of his patient.

Hypoxia will ultimately kill the patient, e.g. by an acute pneumonia bringing on congestive failure due to the increased pulmonary vascular resistance. Energetic measures should be undertaken to prevent such an event, and to provide better ventilation of the lungs. If this can be accomplished, the vasoconstrictive element of pulmonary hypertension is removed. Details of treatment cannot be considered in a work of this size, but we must consider the following general measures:

1. Vigorous preventive and symptomatic treatment of bronchitis, upper respiratory infections, asthma and pneumonia with the proper antibiotics, bronchodilators, steroids, dust-free atmospheres or change of climate. Bronchospasm and infection can be reversed and any half-hearted measures are to be condemned.

2. Avoidance of drugs that depress the respiratory centre, e.g. morphine, codeine, even barbiturates should be used with caution.

3. Measures to improve the ventilatory efficiency, e.g. elevating the diaphragm with abdominal belts, pneumoperitoneum and breathing exercises.

4. Methods to assist ventilation: (a) steam inhalants and expectorants and (b) intermittent or continuous oxygen therapy. It must be noted here that with sufficient retention of carbon dioxide the respiratory centre may no longer be sensitive to carbon dioxide levels but rather to oxygen lack alone. Therefore by providing continuous oxygen therapy, one can remove the anoxia and so leave no stimulus to the respiratory centre, producing respiratory depression. Carbon dioxide levels progressively increase and we are then faced with the problem of carbon dioxide narcosis.

5. Measures to improve the pulmonary circulation. As has been mentioned, cardiac strain due to long-continued pulmonary hypertension is a late and serious development in emphysema. By improving ventilation we hope to reduce the pulmonary hypertension somewhat, and so ease the burden on the right heart. Some authors indicate venesection if the heart is overloaded. However, although the secondary polycythemia, with its increased blood volume and viscosity, call for increased cardiac work, venesection should be avoided, since by lowering the hemoglobin, the heart is called on to a greater cardiac output which

only results in increased pulmonary arterial pressures and decreased arterial oxygen tension. Furthermore it is too sudden and drastic a means of lowering venous pressure, if it is misjudged. Diuretics, low-salt diet, and digitalization are indicated early in signs of cardiac strain.

The prognosis in emphysema complicated by pulmonary hypertension and incipient right heart failure, is poor, but by prompt and adequate relief of hypoxia the progress of the disease is retarded and the patient's life made more comfortable.

Acknowledgement

The author wishes to thank Dr. C. R. Woolf and Dr. R. W. Gunton for their kind help and suggestions in the preparation of this paper.

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Syphilis:—

Syphilis is still a common disease. Since the advent of penicillin the incidence of syphilis per 100,000 population has been cut in half. Today we tend to think that it is a rare disease yet in 1953 156,000 new cases of syphilis were reported in the United States. Since 1953 many hospitals have discontinued their routine serological tests for syphilis and this tendency is on the increase.

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MOTION SICKNESS

G. J. DONSKY, 6T1

EARLY in World War II, it became apparent that the moving of large numbers of men by sea and air and through combat areas might be attended by an increased incidence of motion sickness, and as a result, the problem began to receive, for the first time, comprehensive attention. Basically, the equilibratory sense organs of the labyrinth and otolith organs and semi-circular canals are stimulated by linear acceleration or by angular acceleration as in rotations, swaying or rolling motions.

AETIOLOGY:

(i) CHARACTERISTICS OF EFFECTIVE MOTION

An essential feature of an effective motion is a repetitive change of velocity. By experimentally varying the time interval between acceleration, it was proven that the time characteristic of a motion rather than its violence is the feature relevant to motion sickness. This phenomenon can be observed in vehicles and movements which yield large accelerations and long phases are apt to be very productive of motion sickness. When the total wave duration is held constant, the total energy per wave is a more potent factor than the interval between accelerations.

(ii) VESTIBULAR FACTORS

Motion sickness can be produced by either angular or linear accelerations. When it is evoked by the former, the semi-circular canals appear to be primarily involved; if produced by vertical or horizontal acceleration, the utricles are stimulated. Labyrinthectomy or section of the vestibular nerves abolishes the susceptibility to motion sickness, and deaf-mutes who have underdeveloped labyrinths, or infants who have not commenced to walk and whose labyrinths are not functioning fully, do not suffer from motion sickness. In the face of the evidence that head position, regardless of body position, is such a prepotent determinant of the incidence of motion sickness, all extra-labyrinth stimulations fade into relative insignificance.

(iii) VISUAL FACTORS

Although visual stimuli may facilitate the production of sickness by motion or even provoke it in the absence of labyrinth stimulation, visual influences are more apt to ameliorate the effects of motion: For example, when aircraft pilots fly as passengers, they tend to show increased susceptibility to motion sickness. On the other hand, viewing the motion picture of a ride in an airplane, which would cause sickness if experienced, may give rise to nausea.

(iv) CENTRAL NERVOUS MECHANISMS

On exposure to an effective type of motion, the sense organs of the non-auditory labyrinth discharge repetitively in some particular pattern to the brain. The maintenance of the bombardment of the afferent impulses seem to be essential for the development of motion sickness. The subjective experience called nausea, the visceral changes mediated through the autonomic efferent pathways and finally the integrated somatic nervous discharges to the skeletal muscle which cause vomiting all result from the activation of some of the central mechanisms by what appears to be an instance of temporal summation of afferent impulses.

(v) BODILY CHANGES EVOKED BY MOTION

Some workers have thought that a number of bodily disturbances mechanically evoked were primary contributing causes of motion sickness. For example, it has been suggested that motions of a ship cause gross movements of the heavy

abdominal viscera. However, no correlation could be found between susceptibility and lability of the viscera. People who indulge in horseback riding and therefore subject themselves to jolting movement, or who indulge in strenuous forms of play do not develop motion sickness.

(vi) PSYCHOLOGICAL FACTORS

Many writers have attempted to consider emotional factors as an aetiological factor in precipitating motion sickness. They support this hypothesis by reference to the following:

(a) findings of emotional instability and neurotic traits in very susceptible individuals.
(b) claims that apprehension or fear cause or precipitate symptoms of motion sickness.
(c) the precipitation of seasickness or airsickness by disagreeable sights or odours.
(d) the fact that individuals may, through a process of conditioning become sick on motionless vessels or aeroplanes and, in a few cases, even by looking at or thinking about a moving vehicle or a rough sea.
(e) a supposed correlation between mental or physical activity and a diminution of susceptibility.
(f) stories of sailors and air-gunners incapacitated by motion sickness who apparently recovered or at least responded effectively to an urgent call to action.
(g) reports of the efficacy of non-specific agents such as lactose placebo in preventing motion sickness.

However, the results of adequately controlled studies do not permit the conclusion that psychological factors are of importance in the aetiology of motion sickness. But such factors may exert an influence after the sickness has developed, for it is well known that they affect the behaviour of individuals during the course of any disability.

(vii) INDIVIDUAL PREDISPOSITION

The belief that susceptibility to seasickness is confined to a relatively small fraction of the population has been dispelled. In fact, it appears that a person may be resistant to one type of motion, but not to another. For example, some tolerate the motions of small boats, but will become sick on larger vessels, some get sick on the ordinary swing, but not in an aeroplane or ship. All that can be said is that susceptibility appears to depend on a rather specific constitutional capacity to respond to certain patterns of vestibular stimulation. When the exigencies of World War II evoked an urgent demand for factual information on this subject, it was discovered that almost every normal individual can be made sick by some type of motion.

Clinical Manifestations

The symptoms of this sickness may come on without warning. The victim may have been previously in good spirits, but suddenly becomes quiet and subdued. At this point, the patient may feel nauseated and aware of excessive salivation. Mental depression and anorexia are almost constantly present. Vomiting may take place with a mild headache. Pallor, chiefly facial, and cold sweats are common, but true vertigo is rare. There are no characteristic objective signs. Occasionally there may be a drop in systolic blood pressure accompanied by tachycardia or slow pulse rate.

Prophylaxis and Treatment

Head rests in aeroplanes have significantly decreased motion sickness. Travellers should place their heads firmly against the back of the seat, thereby lessening forward and backward movements. Fixing the eye on a definite object in space is of real help. If the eye shifts with the position of the aeroplane, the

earth and sky will swim past the eye and produce dizziness or nausea, as when one whirls rapidly on a piano stool. Travelling by night decreases the chance of acquiring motion sickness since the visual factors are removed. In smaller vehicles, sitting near the centre of gravity often helps. Intake of food and drink should be moderate and gas-forming foods and beverages should be avoided before travel. Repeated exposure to motion often results in a development of tolerance to motion sickness.

Drugs which depress the vomiting centre are the most generally effective treatment. Chlorbutol has been used to depress the vomiting centre by central action. The most effective central depressant of vomiting is hyoscine. It is effective when taken by mouth in a dose of 0.6–1.2 mg. The effect lasts about six hours, after which a further 0.3 mg. may be taken.

Cyclizine (Marzine) in 50 mg. tablets is less apt to cause drowsiness than any other remedy. Its effect is instantaneous and its duration of action is four hours. It should be given 15–20 minutes before entering a vehicle. Bonamine has a twenty-four hour effect, but it causes drowsiness.

In nervous people or patients with other organic disease, such as cholecystic disease, where vomiting might induce relapse or recurrence of disease, a sedative is also desired. Dimenhydrinate (Dramamine) in 50 mg. tablets is indicated.

In severe cases of motion sickness, where vomiting is severe and prolonged, Marzine and/or Dramamine in rectal suppositories may help. In all cases of severe motion sickness, bed rest and replacement of fluids by mouth or intravenously are essential.

The mode of action of these drugs in relieving or preventing motion sickness is obscure. It is probably due mostly to a central action which blocks the spread to medullary centres of nervous impulses arising from over-stimulation of the vestibular apparatus of the inner ear. It may also be due in part to suppression of excessive vagal activity.

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Tic Douloureux and Dilantin:—

Thirty patients were treated with Dilantin 0.1 Gm. three times a day with surprising results. The great majority responded in 48 hours.

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Schizophrenia:—

It seems that we are getting closer and closer to attributing schizophrenia to metabolic causes. Winter and Flataker report that an extraction of plasma from schizophrenic patients produces the same effects in experimental rats as the injection of LSD (lysergic acid).

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RH HAPTEN

A. F. LEWIS, 6T2

Rh incompatibility in pregnancy, with the resultant deaths of affected infants, has been so well publicized recently that even the layman is somewhat familiar with this problem. Yet it is scarcely twenty years since Landsteiner[1] and Wiener[2] discovered the Rh property of human blood by means of immune sera prepared from the blood of Rhesus monkeys. The Rh factor was found in the blood of about 85% of white individuals and was independent of the ABO and MN types. Individuals who have this Rh factor are referred to as Rh positive, the remaining 15% being Rh negative.

Wright[3] describes what may happen when an Rh negative woman is pregnant with an Rh positive foetus. He says, "Cells containing the D agglutinogen pass across the placenta from the foetus to the mother; the latter responds by forming anti-D agglutinins which return to the foetal circulation and tend to destroy the foetal red cells." The amount of damage to the foetus depends on the amount of anti-D agglutinins formed by the mother and the ability of these agglutinins to cross the placenta. Usually, the first infant is not affected, but in subsequent pregnancies the destruction of foetal red cells may become more and more severe. If the woman has been immunized previously by a transfusion of Rh positive blood, a dangerously high response may occur during the first pregnancy. It should be emphasized, however, that in the great majority of matings between an Rh negative woman and an Rh positive man, agglutinins are not formed and normal offspring are produced.

The agglutinogens of the foetus can be considered as antigens to the mother. An antigen has been defined by Potter[4] as "any substance whose introduction into the tissues of an animal results in the appearance of antibodies in the blood serum after a suitable length of time". How the Rh antigen enters the circulation of the mother during pregnancy is not known (Kabat[5]). Dippel[6] and Wiener[7] have advanced the theory that there is an actual break in the placental wall. The mother responds to the Rh antigen by forming antibodies which pass back through the placenta and into the blood of the foetus, causing destruction of its red cells. Some of the clinical effects which occur in erythroblastosis foetalis are haemolytic jaundice, anaemia, an increase in the nucleated red cells, and in severe cases, kernicterus and death.

For live-born infants the established treatment of erythroblastosis foetalis is exchange transfusion with Rh negative blood. For severe cases in which the foetus does not live to term there has been no successful treatment. The reports of Carter, Williamson, Loughrey and Ingram[8] and of Carter and Lewis[9] on clinical trials of a preparation called "Rh hapten" indicate that it can dramatically decrease the severity of erythroblastosis foetalis.

In 1947 Carter[10] made a preparation from Rh positive red cells which, upon administration, was found to reduce the titre of Rh antibodies in human anti-Rh serum. She called this preparation "Rh hapten" because it acted in the same way as other haptens, i.e. it was not antigenic by itself but when it was combined with a protein such as albumin, it possessed antigenic properties.

Preparation of "Rh Hapten"

Rh positive cells of any ABO group are pooled and to these cells are added two volumes of 95% ethanol. The mixture is stirred vigorously for five minutes and then is allowed to stand overnight at room temperature. The ethanol causes a pre-

cipitation of the proteins and also removes carbohydrates. The mixture is filtered under suction and the filtrate is discarded. Two volumes of methylene chloride are added to the precipitate, stirred for five minutes with an electric stirrer and then allowed to stand overnight at room temperature. The methylene chloride solution, containing dissolved lipids, is separated from the precipitated material by filtration under suction and the filtrate is evaporated to dryness by a current of air at room temperature. The residue contains a crude mixture of lipids and is called "Rh hapten" by Carter[10, 11]. The yield from four litres of blood is about five grams of crude lipid. This material can be stored in the refrigerator for at least three months without loss of activity.

Chemical Properties

The lipid preparation is insoluble in water and soluble in warm 95% ethanol, in ether, in chloroform, and in acetone. It gives a positive Liebermann-Burchard test which indicates that cholesterol and/or another unsaturated sterol are present. Saponification yields 50% non-saponifiable material but in the process most of the activity is lost; what little remains is found in the non-saponifiable fraction. The preparation contains about 2% nitrogen and from 0.5 to 1% phosphorus; the biuret and Molisch tests are negative. The ingredient which is active as an Rh hapten has not been isolated from the lipid mixture.

Clinical Trials

"Rh hapten" was originally administered by intramuscular injection of an alcoholic solution (Carter *et al.*[8]). Oral administration has now been shown to be equally effective (Carter and Lewis[9]). The criteria used in choosing patients has been as follows: (1) The husband must be homozygous Rh positive, as far as can be determined. (2) The woman must have an Rh antibody titre which has been determined by at least two different laboratories. (3) The woman must have lost one or more infants because of Rh incompatibility and resultant erythroblastosis, as determined by blood studies and autopsy. (4) The woman must not be pregnant at the beginning of treatment and must plan to avoid pregnancy until her antibody titre is zero as determined by the method of Lewis and Carter.[12] This method differs from those commonly used in routine clinical work and gives different results. Indeed, the usual clinical methods may show no change in the antibody titre of the serum of a patient undergoing treatment with "Rh hapten", while at the same time the method of Lewis and Carter may indicate a marked decrease in the titre of this serum.

The amount of the lipid preparation administered orally prior to pregnancy is 100 mg. per day. Upon the commencement of pregnancy the dosage is increased to 200 mg. per day. When Carter and Lewis[9] published their report, only eight of the seventeen cases under study had completed pregnancy. Since that paper appeared the other nine cases have been completed and there has not been one infant lost by a mother given the lipid preparation orally prior to and during pregnancy. Each of the seventeen women showed a fall in antibody titre and all the titres reached zero in four months or less (as determined by the method of Lewis and Carter[12]). Figure 1 illustrates the typical decrease in antibody titres which occurred.

Only a few other investigators have attempted to use "Rh hapten" clinically. Ehrenberg[13] and Schubert and Grunberg[14] have reported successes; Wolf *et al.*[15], Marsters *et al.*[16] and Spurling *et al.*[17] have reported failures. These failures are not surprising because these latter groups reported that they gave much less "Rh hapten" than that recommended by Carter *et al.*[8], and they did not begin administration until pregnancy was well advanced.

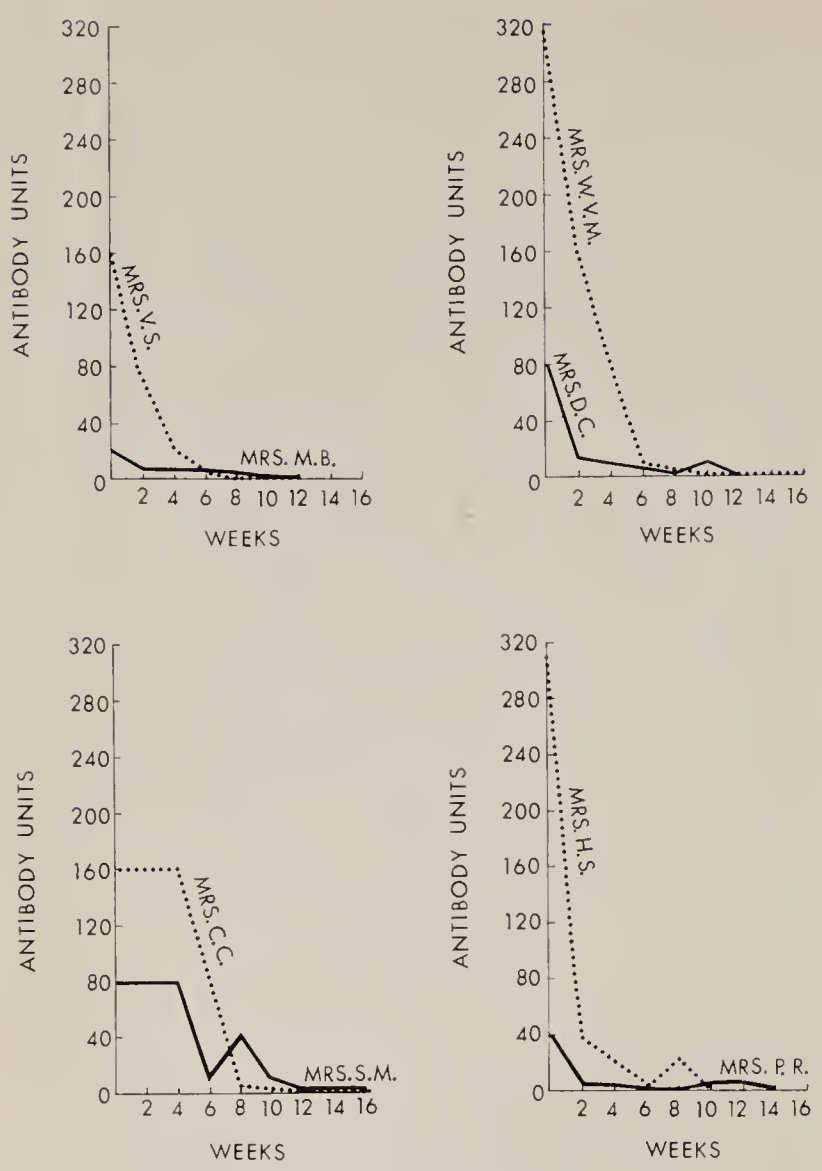

Fig. 1.—Rh antibody units.

CHOLESTEROL CONTENT

The lipid preparation contains more than 35% cholesterol and other sterols. Hence, with the daily administration of 200 mg., a patient receives about 70 mg. of cholesterol per day. Although this is not a large amount, recent interest in atherosclerosis led to a study of the serum cholesterol levels of women receiving the lipid preparation (Lewis and Carter[18]). These levels were determined every fortnight over a period of six months. The groups of subjects used in the study were: (1) 38 pregnant women who were taking the lipid preparation orally, (2) 23 non-pregnant women who were taking the lipid preparation orally, (3) 6 pregnant women who were not taking the lipid preparation, and (4) 4 non-pregnant women and 7 males who were not taking the lipid preparation. There were no significant differences in serum cholesterol levels in any of the groups. It was concluded that the recommended dosage of the lipid preparation had no apparent effect on the level of serum cholesterol.

WORK IN PROGRESS

Recent investigations by the author have been concerned with two problems: first, study and refinement of the Lewis and Carter[12] method of determining antibody titres and second, the development of a satisfactory quantitative assay of Rh hapten activity. These problems are interrelated because the antibody titre method is presently used in the routine assay of Rh hapten activity.

The first problem requires study for two reasons. (1) It is well known that routine Rh antibody titrations performed on the same blood sample by different laboratories are rarely in agreement. The need for standardization of these titration methods is apparent. (2) The Rh antibody level determined by routine clinical titrations does not give a satisfactory prediction of the severity of erythroblastosis foetalis. For example, a patient with a weak titre of antibodies detectable only to a dilution of 1:2 may have a severely affected child, whereas another patient with a stronger 1:16 titre may have a child who is only slightly affected. These discrepancies are not understood at the present time.

The reasons for the investigation of the problem of a quantitative assay of Rh hapten are more obvious. The hapten must be assayed for activity before administration and, in addition, assay is essential in assessing the success of attempts to fractionate the crude material and isolate the active ingredient.

SUMMARY

A lipid fraction prepared from Rh positive red blood cells contains material which has the properties of Rh hapten. If this lipid preparation is administered orally before and during the pregnancy of an Rh negative woman bearing an Rh positive foetus, the chance of obtaining a

live-born infant with no residual defect is extremely good.

ACKNOWLEDGEMENTS

The author wishes to thank Dr. J. M. Fisher and Dr. G. E. Connell for their encouragement of his work.

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NITROGLYCERINE:—

Before patients are placed on nitroglycerine for anginal attacks they should be instructed in its use. Several points should be stressed:

1. Tablets should be fresh as they lose their potency with time.
2. They should be chewed and the saliva retained in the mouth for a minute.
3. They should be used as often as necessary, and even as a prophylaxis. They are not habit forming, and tolerance does not develop.

Evans, W., B.M.J. 1:249, 1959

PROMAZINES AND HYPOTENSION:—

Be careful of the hypotensive effects of promazine and its derivatives. Although these drugs are used extensively for psychiatric indications this sometimes fatal side effect is seen only when there is associated disease especially of the heart or liver. For example, many physicians readily prescribe these drugs for the emesis accompanying myocardial infarction. Warning symptoms are restlessness, nervousness, apprehension as well as the signs and symptoms of peripheral vascular collapse.

Kaplan, N. M., A.M.A. Arch. Int. Med. 103:219, 1959

CEREBRAL PALSY

MISS SYLVIA FINE, 6T0

CEREBRAL palsy is a loose term which is used to describe neurological disorders of the immature brain's motor system which are irreversible and non-progressive. Sensory or intellectual defects may occur as well as motor defects. It occurs about 1 in 600 live births and is therefore a problem for the general practitioner, the obstetrician, the pediatrician and the neurologist.

The etiology and the pathogenesis is obscure. Pre-natal causes include maldevelopment of the nervous system, rubella in the mother during the first trimester, X-ray irradiation of the fetus, toxemia of pregnancy. Natal causes include birth injury resulting in cerebrovascular accident or anoxia; anoxia from other causes such as over-sedation. Among post-natal causes are kernicterus from erythroblastosis fetalis; severe infections such as meningitis, encephalitis; convulsions. Some studies implicate advanced maternal age, previous poor obstetrical history and hereditary factors among etiological agents. Cerebral palsy may also be found in association with congenital abnormalities such as microcephaly.

It is not surprising that with so many causes there is no one pathognomonic lesion to be found. Areas of gliosis and or atrophy of the cortical convolutions have been described. The location of the lesion determines the clinical picture.

Classification

1. PYRAMIDAL SYSTEM INVOLVEMENT
   - (a) *Spastic diplegia*
   - (b) *Hemiplegia*
   - (c) *Double hemiplegia*
   - (d) *Quadriplegia*
2. EXTRAPYRAMIDAL SYSTEM INVOLVEMENT
   - (a) *Athetosis*
   - (b) *Chorea*
   - (c) *Tremors*
   - (d) *Rigidity*
3. CEREBELLAR INVOLVEMENT

PYRAMIDAL SYSTEM INVOLVEMENT

Pyramidal system involvement results in spastic cerebral palsy, the largest group of cerebral palsied. This group can be further classified according to the number of limbs involved, so that there are diplegics, monoplegics, quadriplegics, hemiplegics and paraplegics. Quadriplegia with more leg involvement than arm involvement is the common situation. In the spastic group, atrophy is not a feature, although an affected limb will not grow to the same size as a normal limb. There is never complete paralysis since there are always some patterns of movement in which the affected muscles will work, even if they cannot be voluntarily contracted. Bulbar musculature is sometimes involved as well as the limbs.

(a) *Spastic diplegia*

These children exhibit increased deep tendon reflexes, increased muscle tone and muscle weakness. The affected legs are adducted and extended. The feet are plantar-flexed and inverted. This position results in a scissors gait when the child walks i.e. the legs are crossed and the heels are off the ground. Hands and arms are affected to a lesser degree than the legs, but will also show weakness, stiffness and spasticity. Sphincter function is not usually impaired. Not uncommonly dysarthria, ataxia and hypotonia may be present. Athetosis of the face, tongue and hands may be prominent. Intelligence is often deficient.

(b) *Hemiplegia*

This condition is characterized by increased reflexes, extensor plantar response and weakness. Muscle tone may

be normal. Sensory defects are not uncommon in this group. An homonymous visual field defect may be present. Decreased superficial sensation, defective proprioception, two point discrimination and stereognosis may also be found. Athetosis of the affected arm can occur. The wrist is usually flexed and the metacarpal-phalangeal joints are extended. Intellectual functions are often impaired. There is a 35 to 50% incidence of convulsive disorders in this group. These children will often improve over the years as they learn to compensate for the sensory defect.

(c) *Double Hemiplegia*

This is the same condition as unilateral hemiplegia except that there is severe arm involvement and severe mental retardation and many associated defects such as blindness and convulsive disorders.

(d) *Quadriplegia*

In this group, all the limbs but not the bulbar musculature are involved. It can be caused by a bilateral cerebral lesion or by a cervical cord injury and care should be taken to rule out a treatable cord injury in these cases. Cord lesions will usually show sphincter disturbances and a sensory level.

EXTRAPYRAMIDAL SYSTEM INVOLVEMENT

With a lesion of the extrapyramidal tract, the synergistic action of muscle groups is lost.

(a) *Athetosis*

This is the common disorder of the group. It is characterized by slow, writhing, twisting movements of limbs and face. Voluntary movement produces an overflow phenomena—i.e. muscles not necessary to the movement will contract. Muscle tone is usually normal, but may show lead pipe rigidity. Sensation is normal. Reflexes show no consistent abnormalities. The plantar reflexes are downgoing. Athetosis of the bulbar muscles leads to slurred inarticulate speech, drooling and facial grimaces. Hearing defects, ocular palsies can also occur, especially if kernicterus is the cause. As a rule, intelligence is spared.

(b) *Chorea, tremors* and *rigidity* may be found in conjunction with athetosis. More rarely they may each form the primary clinical picture.

CEREBELLAR INVOLVEMENT

Lesions of the cerebellum give rise to a picture of ataxia, incoordination and hypotonia. Tendon reflexes are present. Nystagmus may be found. There is often intellectual impairment and speech development is often retarded. Hearing is disturbed when the vestibular tracts are involved. Cerebral diplegia may be an associated finding.

DIAGNOSIS

One must realize that these clinical syndromes are often difficult to differentiate even when fully developed because of overlapping of signs; there are also varied degrees of involvement. Diagnosis with certainty cannot be made until the child is approaching 8–9 months of age and often in mild cases not until 3–4 years. (It should be noted that infants exist on a brain stem level until about 5 months.)

Certain circumstances should alert the physician to the diagnosis:

1. A history of rubella (German measles) or serious illness in the mother during the first trimester.
2. Irradiation of the fetus during pregnancy.
3. Difficult, long labour with prolonged anoxia and traumatic head delivery.
4. Kernicterus, as may occur with erythroblastosis fetalis.
5. Congenital defects such as microcephaly.
6. Poor reflexes e.g. sucking and difficult breathing and difficult swallowing.
7. Lack of movement of one or more limbs.

8. Delay in motor development, e.g. head erect, sitting, crawling, etc.

Before making a diagnosis of cerebral palsy it is necessary to rule out progressive disease which may or may not be amenable to treatment. The child may have to be seen over a period of several years before a decision is final. Cervical spine injury, cerebral space-occupying lesions, demyelinating disease, lipid storage diseases and mental retardation may mimic cerebral palsy.

Management

When the diagnosis is made, a period of assessment by a team consisting of the doctor, physical therapist, occupational therapist, speech therapist and psychologist, should follow and a decision is made on the management of the child. Of every seven cases of cerebral palsy, one will be so mild as to require little or no treatment; two will require treatment and will benefit by it; two will be so severely affected that institutional care will be necessary and one will die in infancy.

Management of the family with a cerebral palsied child is important. Parents have preconceived ideas and attitudes towards illness and defects and often think that the cerebral palsied child is a punishment for some misdeed, either real or imagined. The mother may feel that something she did during the pregnancy actually harmed the child and that she is directly responsible for its condition. Parents will accuse each other of having bad stock and transmitting a defect. The obstetrician may be accused of negligence in handling the child. Naturally such strong feelings influence the parent-child relationship. The parents' attitude will range from outright rejection to zealous over-protection. In turn the child will develop confused attitudes about himself and resentment, anger and dependency towards the family. Other children in the family will be drawn into the emotional entanglement and be affected by it. The parents must receive sensible advice from their physician and, if necessary, they should be referred to a social worker in this field. The parents must be assured that they are blameless since cerebral palsy is an accident of nature and not a form of retribution. Even with a good psychological background, these children may suffer emotionally when they realize that they have a handicap and that they are different. The family must accept the handicapped child and his limitations so that he gets the normal family affection, so that a realistic future can be planned, and so that other members of the family are not neglected.

Treatment begins with the pre-school child and may be carried on almost to adulthood. During this time, the child must be educated and, if possible, trained for a job and helped to become a useful member of society. Since large sums of money are contributed annually for the treatment of cerebral palsy, some of the expected benefits of these programmes should be mentioned. The child who can learn to look after its own needs such as dressing, feeding, washing, etc. frees the mother for other duties in the house. If the young person can be trained for a job, then he is an employable member of the community and often can earn part or all of his upkeep.

Segregation of the cerebral palsied from the rest of the population is inadvisable if one hopes to fit them into our society. Schooling and job training should be acquired in the normal situation or one close to it if possible. In a large city there may be a school designed for the handicapped. In Toronto, Sunnyview School combines treatment and public school education for the handicapped children.

In smaller centres, arrangements can sometimes be made with local school boards to take these children into regular school classes and their treatment can be carried out at home or at local clinics or hospitals. One finds that the friendships, discipline and competition of the school-

room help the cerebral palsied child to develop the social and working skills which enable him to accept his limitations and yet take his place in society.

Treatment is carried out mainly by physiotherapists, occupational therapists and speech therapists who train the child in the control of posture and movement, the development of hand skills, self-help activities and the correction of speech defects.

SCHOOLS OF TREATMENT

In the United States and Europe, workers in cerebral palsy have developed many principles and philosophies concerning the treatment of this condition. The efficacy of each of these schools of treatment is difficult to judge since the criteria of successful treatment have not been clearly set down; comparisons are beyond the scope of this article.

1. *Temple Fay* believes that with cortical injury and paralysis of voluntary movement, lower levels of activity originating in the brain stem must be made to function before deformity and structural changes make movement impossible. When higher centres are out of control, the simple patterns of movement usually seen in early infancy must be learned well before attempting the more complex patterns of crawling or walking. These simple patterns of behaviour are clearly seen in lower forms of life such as amphibians. This hypothesis leads to a treatment consisting of progressive patterns of movement based on simple reflexes.

2. *Kabat* has developed a programme which utilizes heavy resistance exercise given manually by the therapist in order to stimulate the greatest number of motor units and produce maximal activation of the entire nerve pathway. This method relies on the correct performance of simple motions as the first step in neuromuscular education.

3. *Phelps* has attempted a detailed classification of cerebral palsy in order to assess the type of lesion and its location as accurately as possible and then uses the media of physical and occupational therapy such as massage, active and passive movements, balance training etc., to teach the child control of his musculature.

4. *Deaver* uses a functional approach. The first training for the child should be in the four basic needs of daily living:

(a) self care
(b) ability to walk or travel
(c) maximum use of hands
(d) adequate speech.

5. The *Bobath* method emphasizes the importance of inhibiting pathological tonic reflexes in order to obtain purposeful coordinated movements. When spasticity is inhibited, coordination is restored by facilitating the righting reflexes and equilibrium reaction. Success in this method depends on an accurate appraisal of the patient's reflex behaviour and posture. By placing all of the patient's limbs in the opposite position to their habitual posture tonic reflexes are sometimes released.

These schools of treatment are by no means universally accepted or followed. Therapists and doctors will use some ideas from these methods as well as those gained from personal experience. The combination is adapted for their particular treatment centre and their patients.

SURGERY AND DRUGS

In addition to these basic methods, surgery is of use in carefully selected cases; procedures such as osteotomies and tendon releases are of value in correcting deformity and increasing function; tendon transplants have also been used. In the future, brain surgery such as pallidectomy may be more widely used than at present.

Drugs are used to control infection and convulsions, if present. Phenobarbital should be avoided, since it appears to cause confusion in these children.

Attempts have been made to control spasticity or abnormal movements with drugs. As yet no drug which is clinically acceptable has been found. Work is continuing in this field and Phely reports good results with Soma (N-isopropyl-2-methyl-2-propyl-1, 3-propanediol carbemase).

In conclusion, one should realize that cerebral palsy is not a rare condition, that it presents a varied clinical picture and that there is no cure. Patients and their families can often be helped to accept the limitations imposed by the condition and to make good use of all assets.

Acknowledgement

The author wishes to thank Dr. J. S. Prichard, Hospital for Sick Children, for his comments on this article.

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CAMSI CONFERENCE

BASIL ORCHARD, 6T1

The Canadian Association of Medical Students and Internes has just concluded one of the most active and interesting years in its history. This became evident during the annual conference held in the Senate Chambers of the University of Toronto, October 12–14. The last day started its afternoon session at least two hours behind schedule, and several points of new business had to be dealt with. Caucuses and committee meetings were held in the small hours of the morning as there was no time during the day. Through all this hurry and bustle came the reports of CAMSI's progress during the last year and the decisions on the direction of its efforts for next year.

We heard that a brief on the subject of income tax was presented to Finance Minister Fleming, pointing out the difficulties and expenses of a university student. It reasoned that these were already so great that it is unfair to add to them by taxing him and his parents on money spent on his education. Thus all fees and expenses for books and instruments should be deductable. This proposal was rejected by Mr. Fleming and, as a result, copies of the brief were taken to the members of parliament from each of the university centres. The question was raised on the floor of the house by Mr. Hellyer but no concession was made. The revision and representation of this brief will be undertaken by the new National CAMSI Executive and the University of Ottawa with the assistance of NFCUS next year.

The problem of increasing the interne stipend to a national minimum level has been attacked whole-heartedly during the past year. Interne committees have been set up and have functioned effectively at University of Western Ontario, McGill, University of Montreal, Laval, and Toronto. The rest of the centres in the country are making the formation of these committees a project for next year. The Canadian Medical Association was approached and as a result, passed a motion approving the principle of increasing the level of interne remuneration. The Ontario Medical Association was also approached, with even greater effect. They approved the figure of $150 per month plus room and board, or $200 per month without this accommodation, which was set as CAMSI's goal at the 1958 Conference. The Local CAMSI Officers at each school also approached the hospitals directly. This resulted in increases in the stipend at Winnipeg, London, Montreal, Quebec, Halifax, St. John, N.B., and at one of the hospitals in Toronto.

The CAMSI Interne Placement Service also reported a successful year. Some nine schools participated and 89.7% of the applicants obtained their first choice of hospital. 7.1% were placed in their second choice. Six hospitals obtained their full quota of internes. This shows an increase of five hospitals from the past year. CAMSI Interne Placement Service also inquired as to the advisability of an earlier starting date for junior internes, and received approving replies from the hospitals. The difficulties encountered by hospitals in changing their entire junior, senior and resident staff on the same day have long been realized, but this is the first step that has been taken to remedy the situation.

Another of CAMSI's interests is low cost, dependable insurance for its members. Thus, some five years ago, CAMSI assisted in the formation of a life insurance company which would handle the CAMSI Life Plan. The report of the National Director of CAMSI insurance showed that there is now some $39,-000,000 of CAMSI insurance in force. $25,000.00 was paid in claims during the past year. This plan has proved satis-

factory to the company and extremely valuable to CAMSI members, as can be seen by the figures.

A preceptorship plan offering students the opportunity to spend time with a general practitioner during the summer was pioneered in Toronto two years ago. This year it was offered at University of Alberta, U.W.O., Toronto, Queens, Montreal, Laval, and Dalhousie, and was felt to be of great value to those students and preceptors who participated.

A student exchange programme was set up with the International Federation of Medical Students Associations, and as a result seven Canadian medical students spent the summer in Europe, Scandinavia and the British Isles.

A summer employment survey was carried out by University of Ottawa which proved of great value to students seeking employment in hospitals. This survey listed jobs available across the country and will be expanded next year to include jobs in laboratories and government agencies.

The Frosst trophy for the best undergraduate medical journal was won by U.W.O. and the Grant Medal for the best article by an undergraduate was presented to Dr. Hugh Curry, of Toronto.

In many schools across the country, reprints of examinations for the last ten years were produced and distributed to CAMSI members free of charge. The reprints of the Dominion Council examiniations were distributed to all fourth-year students in Canada.

The University of Manitoba committee has worked with Dr. L. O. Bradley, Chairman of the C.M.A. Committee on Approval of Interneships, and with local internes, to produce an interneship evaluation questionnaire. This will be distributed to internes in the 1959–60 class and will provide the C.M.A. and CAMSI members with some method of deciding upon the relative merits of the various hospitals.

An attempt to lift the barriers to interning in the U.S.A. was unsuccessful. The College of Physicians and Surgeons was adamant in its stand that after 1961, any applicant for licensing examinations must have had a least one year's interneship in Canada. However, more and more information is being accumulated by CAMSI to show that most of these students who go to the U.S. to interne are citizens of the U.S. who have come to Canada to medical school, or have decided to do all their postgraduate training in the U.S. These facts will be placed before the College again this year.

University of British Columbia presented a final report on the need for student mental health services in all universities, and the good results obtained at those universities which have these clinics. The big project for next year at U.B.C. is to begin the work of setting up a pilot clinic.

Subscription privileges at low rates were obtained for CAMSI members to approximately fifteen medical journals.

CAMSI this year offered to its members a student microscope which has been duly approved at Toronto, Dalhousie, U.W.O. and Queens. The object was to provide the most inexpensive but adequate microscope for those who did not wish to buy expensive instruments. The National Executive will continue this project next year.

The medical schools in the Province of Quebec organized an exceptionally fine hospitalization insurance plan somewhat similar to the one available at the University of Toronto before the government plan came into effect. This is meeting with success as it is fulfilling a need in this province.

The National Executive from Toronto has now turned over the guiding reins of this active and effective organization to the new National Executive from Queens. This was symbolized at the end of the conference by the past president, Dr. Jules Harris, giving the chairmanship of the meeting to Sandy Scott, the new president.

NEWS AND NOTES

Alpha Omega Alpha Honour Medical Society has had a chapter at the University of Toronto since 1906. The AOA is a student organization whose intention is to foster high standards of professional idealism and scholarship. It has chapters at all the principal Medical Schools in Canada and the United States. Students are elected to membership in the third and fourth years only, and entrance is dependent upon academic achievement, personality and character. The activities of AOA consist of bi-monthly meetings held during the winter session at which papers are presented by the undergraduate members. A banquet is held each year at which an address is delivered on some subject of current interest. Those elected for the coming year are: K. Newman, J. K. Nicholson, J. Wait, P. Dent, R. G. Lee, P. Adam, L. E. Dorfman, O. Veidlinger, H. Weber, H. Crystal, D. Varadi, J. Shugar, J. Schatzker, P. Citron, M. L. Jerry, H. Singer, C. H. Tator, M. Sazant. The executive of AOA is as follows: B. Goldman (Pres.), M. Barkin (Sect'y), R. Matthews (Treas.).

———

Three admission scholarships were awarded in first pre-medical year: The Medical Alumni Association Award to Mr. R. C. Allin, The Harvey Harnick Scholarship to Miss S. Ernitz, and the Samuel Godfrey scholarship to Mr. M. H. King.

———

Dr. J. A. MacFarlane, Dean of the Faculty of Medicine, was present at the opening of the first Canadian Armed Forces Medical Services Hospital in Kingston, Ont. on October 9. The Tri-Service hospital will be a teaching hospital affiliated under special arrangement with Queen's University.

Dr. Harry Shields Lectureship in Anaesthesia. The first lecture under this foundation was given on October 30 at the Toronto General Hospital. The Lecturer was Dr. H. R. Griffith, Professor Emeritus of Anaesthesia at McGill University. His subject was "The Boundless Realms of Anaesthesiology".

———

The Chairman of the Medical Society Assembly for 1959–60 is Dr. Ian van Praagh, who is now in his fifth year of post-graduate studies in Obstetrics and Gynaecology at the Toronto General Hospital. Dr. Van Praagh was chairman of the Staff–Student Curriculum Committee in his graduating year.

The Honorary Secretary-Treasurer of the Assembly is Dr. Cameron Gray, Class of '39. Dr. Gray was Vice-President of the Medical Society in his third medical year and President of the Society in his graduating year.

———

Dr. E. M. Jellinek, professor of psychiatry at the University of Toronto, received the first Gold Key Award presented by the National Council on Alcoholism of the United States for outstanding service in alcoholism prevention and treatment. The award was received at a dinner in the Waldorf-Astoria Hotel in New York marking the Council's 15th anniversary in October.

———

The Frosst Trophy, awarded for the best undergraduate medical journal in Canada, has been awarded to the University of Western Ontario for 1958–59. Toronto and Ottawa were close seconds. Here is the comment regarding the Toronto Journal: "Coverage not as complete as that of U.W.O. Symposia excellent. Editorials of local interest only."

CAMSI has awarded the Grant Medal to Dr. R. H. Curry of the University of

Toronto 5T9 for the best individual article by a Canadian undergraduate. The medal is named in honour of Dr. J. C. B. Grant, Professor Emeritus of Anatomy at U. of T.

———

Canada's first Hospital for Diabetics is to be built in Toronto. The 60-bed institution will be the result of the dreams and months of work by a committee headed by Dr. Charles H. Best, co-discoverer of insulin. There is no centre in Toronto for diabetic treatment although Toronto is the city in which insulin was discovered. Diabetic Hospitals exist in Copenhagen and Boston, for example. Plans for the hospital are on the drawing board, but they are not final yet because the site is not definite. The Best Institute carries on research into the problems of diabetes constantly, but clinical research now has to be conducted in hospitals all over the city. Dr. W. R. Feasby, Medical Director of the Canadian Diabetic Association, and a Committee member, said that diabetes affects 1.6% of the population of Canada (280,000 cases) and 96,000 in Ontario alone.

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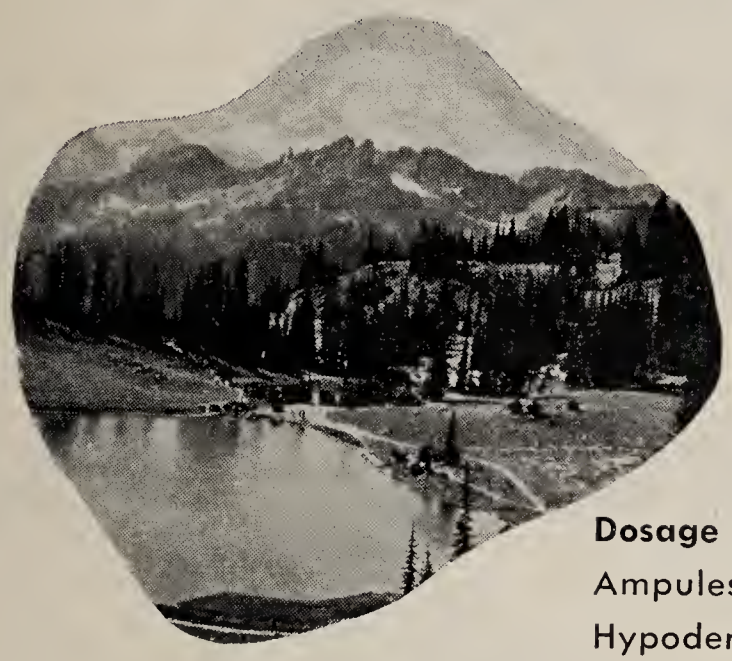

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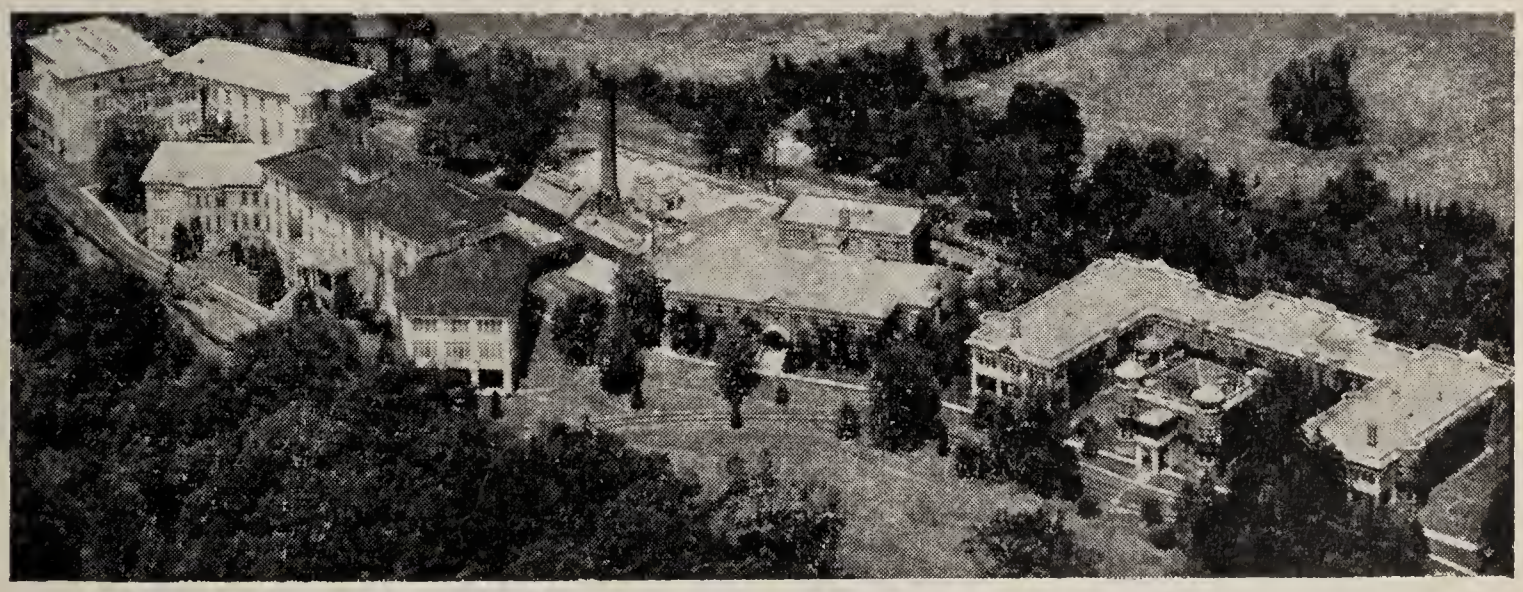

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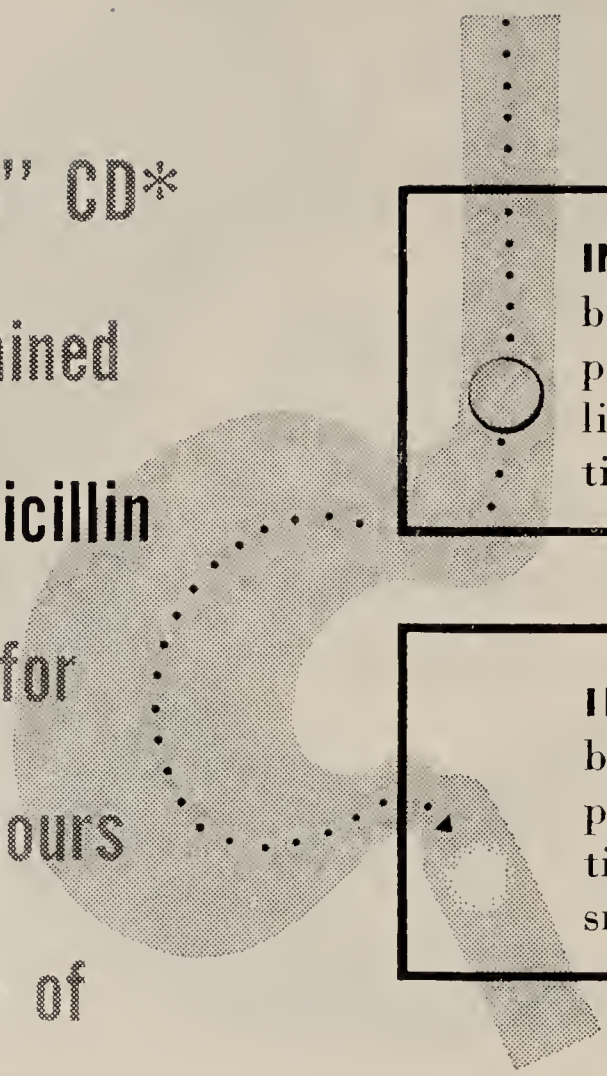
One "Hylenta" CD* tablet maintained effective penicillin blood levels for over seven hours in twenty-six of twenty-seven patients



IN ACID, the tablet base is insoluble to protect the penicillin from destruction.

IN ALKALI, the base disintegrates, permitting absorption from the upper small intestine.

When a combination of a sulfonamide AND penicillin is indicated:

"HYLENTA"-S CD* No. 887

Each tablet contains:

Sulfamethazine..... 0.5 Gm.
Penicillin G Potassium.... 250,000 I.U.
in a *Controlled Disintegration base.

"Hylenta" CD* TABLETS

No. 888
(500,000 I.U. Penicillin G Potassium, supplied in bottles of 12, 100 and 500)

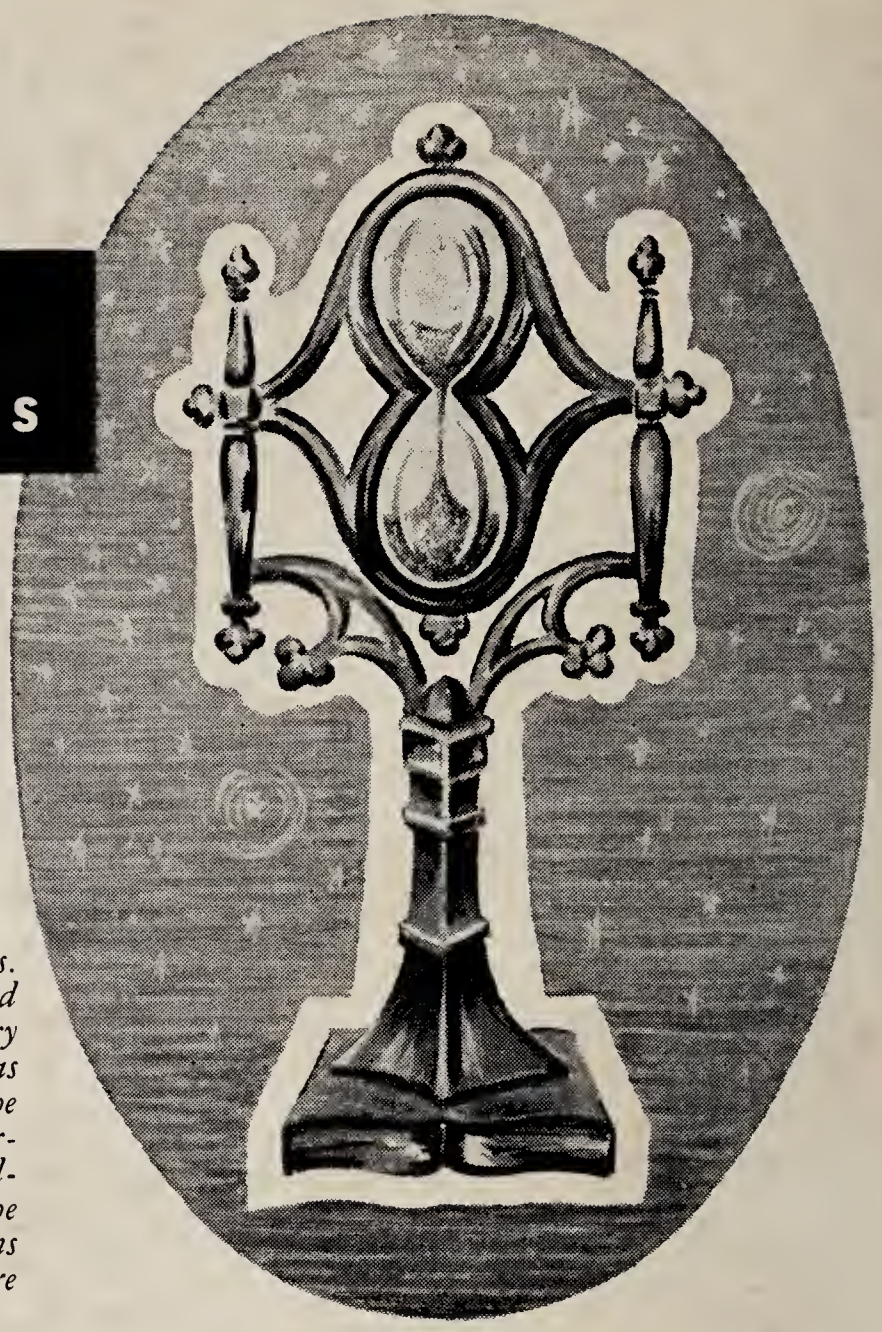
*Controlled Disintegration

Ayerst

Ayerst, McKenna & Harrison Limited, Montreal

111-359

TIME through the ages



HOUR GLASS

Also known as a sand-glass. Thought to be invented about the Third Century B.C. in Alexandria. Was used in churches during the 18th Century to time services. A two-minute sand-glass is still turned in the British House of Commons while "division bells" are being rung.

TIME to study

Your busy day leaves little time to keep informed of medical developments. By using the resources and abilities of your pharmacist, you free yourself of the needless detail and expense of running a dispensary . . . gaining *time* for reading and study.

LET THE PHARMACIST DO ALL YOUR DISPENSING

ONTARIO RETAIL PHARMACISTS ASSOCIATION

THE ONTARIO RETAIL PHARMACISTS' ASSOCIATION